About Face: Molecular Aberrations in Head and Neck Mucosal Melanomas

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Detailed molecular characterization of a large cohort of mucosal melanomas, most arising from head and neck primaries, suggests that chromosomal translocations and other complex rearrangements have prognostic importance. CDK4 amplification is a frequent event in these rare tumors, and CDK4/6 inhibition may represent a rational clinical trial strategy.

See related article by Zhou et al., p. 3548

In this issue of Clinical Cancer Research, Zhou and colleagues (1) report several novel molecular insights with potential clinical relevance in a cohort of mucosal melanomas, largely of primary head and neck mucosal melanoma (HNMM). Using a test set of 65 samples that underwent whole-genome sequencing and a validation set of 80 samples that underwent PCR-based assessment of copy number alterations (CNA) in key loci, they verified prior findings (2) that chromosomal translocations, rather than nucleotide variants, represent the most common somatic variant in this disease type. Interestingly, HNMM with clustered translocations between Chromosomes 5 and 12 were associated with worse overall survival than HNMM lacking this translocation. The loci 12q13–15, which contain CDK4 and MDM2, and 5p15, containing TERT, were the most frequent areas of amplification. CDK4 amplifications were seen in roughly half of the samples, suggesting this may be a clinically relevant therapeutic target for patients with HNMM. To investigate this in an in vivo model, patient-derived xenografts (PDX) from 24 samples were created, and a significant minority had some suppression of tumor growth with the CDK4/6 inhibitor palbociclib. The suppression of PDX growth with palbociclib seemed to be enriched in tumors with CDK4 amplification, strengthening the assertion that this dysregulated pathway represents an important contributor to growth in HNMM.

These findings are a welcome addition to the literature for several reasons. Approximately 20% to 25% of mucosal melanomas respond to anti–programmed death-1 (PD-1) monotherapy and 35% to 40% respond to combined PD-1 plus cytotoxic T lymphocyte antigen (CTLA)-4 blockade, and some responses can be durable (3). Unfortunately, this means most patients still experience primary progression in tumor sites that can cause significant morbidity from local growth and are at risk for life-threatening distant metastases. Secondary resistance to checkpoint inhibitors after initial clinical benefit also remains a significant problem. The work detailed in this issue confirms prior work showing standard molecular therapeutic targets, such as KIT exon 11 or BRAF V600 mutations, are present only in a minority of samples. Thus, most patients with mucosal melanoma who progress on checkpoint inhibitor therapy lack a rational salvage therapeutic option beyond cytotoxic chemotherapy. This work suggests that routine copy number detection in mucosal melanomas can reveal molecular aberrations like CDK4 or MDM2 amplification that may inform the rational selection of clinical trials in the postcheckpoint inhibitor setting. This adds CDK4 to the shortlist of gene amplifications in mucosal melanoma such as ERBB2 (4), which may be potentially targetable via clinical trials. Recent work also links CDK4 expression with reduced effector function of tumor-infiltrating CD8+ T cells exposed to PD-1, which is ameliorated by short-term CD4 inhibition in murine models of non–small-cell lung cancer (5).

More broadly, this work highlights the fact that mucosal melanomas are distinct from sun-exposed melanomas; they are best conceptualized as their long-lost relatives rather than their reclusive siblings. They arise in anatomic primary sites that are chronically exposed to external antigens and must maintain a unique balance of immune surveillance and tolerance. It should not come as a surprise, then, that the pathogenesis of these tumors might involve mechanisms of immune evasion and growth signaling distinct from sun-exposed cutaneous melanomas. The work in this issue suggests we must expand our focus beyond tumor mutational burden to better understand clinical outcomes for patients with mucosal melanomas. The frequency of chromosome-level aberrations was higher and more variable than tumor mutational burden, and the association of breakage-fusion-bridge events in chromosomes 5 and 12 with overall survival suggests a specific association between these genes and poorer immune surveillance. This is consistent with results from a pan-cancer analysis suggesting tumors with increased arm- and chromosome-level CNA may have a more T-cell–depleted immune infiltrate (6). In a melanoma cohort largely comprised of cutaneous melanomas, tumors with higher levels of CNA have a poorer response to ipilimumab (6). It is not clear whether increasing CNA in mucosal melanoma is a universal feature of poorer prognosis or whether PD-1-based therapies can overcome this mechanism of tumor growth. Even the relationship between CNA and tumor immune infiltrates is yet to be established in mucosal melanomas. Given the recent, promising preliminary report of efficacy of combined VEGFR and PD-1 inhibition in mucosal melanoma (7), further work should also investigate whether KDR amplification or other
genes involved with angiogenesis are enriched in certain subsets of mucosal melanoma. Key findings and highlighted follow-up questions are outlined in Fig. 1.

Several important caveats about the findings in this report will inform future lines of inquiry. First, there is a question of generalizability. This cohort focuses almost exclusively on mucosal melanomas that arise from the oropharynx and sinonasal cavities. It is not clear whether gastrointestinal or genitourinary primary mucosal melanomas will harbor similar molecular aberrations like CDK4 amplification or frequent translocations of chromosomes 5 and 12. Similarly large cohorts of these primary mucosal melanomas would be valuable to understand which molecular mechanisms may vary across primary sites. Further, the insights made in this Asian population of patients may or may not be relevant to other ethnic groups like Caucasians, South Asians, and Latinos that also develop mucosal melanoma. A recent trial of adjuvant cisplatin plus temozolomide conducted in a Chinese population (8) demonstrated a large overall survival benefit over IFN and observation that belies the modest response rates in advanced mucosal melanoma cohorts largely assembled from Caucasian populations (9). We must work together to better understand whether the molecular events underpinning mucosal melanoma vary by a patient’s ethnic background.

As with any important work, there are several caveats regarding the therapeutic implications of this report. The prognostic relationship between chromosome-level aberrations and overall survival must be investigated in patients who have been treated uniformly with modern therapies like PD-1 blockade with or without CTLA-4 blockade or combined PD-1 and VEGFR inhibition. The authors highlight the relationship between increased Ki67 and mutations in the nucleoporin gene POM121, but the clinical relevance of this association is not clear from this report. POM121 protein overexpression was recently linked to the progression of high-risk prostate adenocarcinomas (10) via nuclear import of transcription factors such as Myc. In the absence of functional validation of these alterations, it is not clear whether mutations and amplifications represent convergent or divergent biological processes in HNMM. Future work should focus on what role that nucleoporins may play in this disease. Although the data regarding inhibition of CDK4/6 with palbociclib in PDXs are encouraging, one must acknowledge that the 37% rate of “tumor growth inhibition” of PDXs cited in the manuscript is unlikely to directly translate to the same rate of clinical benefit in patients. It does suggest, however, that offering clinical trials of CDK4/6 inhibitors, with or without other potentially active agents, would be reasonable for patients with HNMM refractory to standard agents.

Overall, this work represents an important advance in our understanding of these rare tumors that will lead to additional insights. It encourages those of us who study mucosal melanomas to lead similar efforts in other mucosal melanoma subtypes, and most importantly, offers us a blueprint on how to spur inquiries into rational treatment targets like CDK4 that will lead to more promising clinical trials for our patients.
Disclosure of Potential Conflicts of Interest

A.N. Shoushtari reports receiving other commercial research support from Bristol-Myers Squibb, AstraZeneca, and Xcovery, and is a consultant/advisory board member for Bristol-Myers Squibb, Castle Biosciences, and Immunocore. No other potential conflicts of interest were disclosed.

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References
